REMARKS

Reconsideration of this application, in view of these amendments and the accompanying Request for Continued Examination, is respectfully requested.

I. Status of the Claims

Claims 1, 4-10, 12, 13, 16-33, 36-59 and 61 are pending. Claims 1, 4-10, 12, 13, 20, 22, 23, 30, 33, 36-43, 55 and 56 are amended. Claims 2, 3, 11, 14, 15, 34, 35 and 60 are canceled without prejudice or disclaimer.

Claim 1 is amended to recite that the composition comprises crystals of a pharmaceutically acceptable salt of citalopram, wherein the median particle size of the crystals is at least 40 μm. Dependent claims 12 and 13 are amended accordingly.

Claim 1 (and dependent claims 4-13 and 36-43) are amended to recite tablets rather than solid unit dosage forms. Claims 22 and 23 are amended to recite a "pharmaceutically acceptable salt of citalopram" rather than a "dissolved substance." Claims 41-43 are amended to correct the antecedent basis and dependency of the claims.

Crystallization method claim 20 is amended to clarify the meaning of the claim. The amendments to claim 20 are not narrowing amendments. Dependent method claims 30, 33, 55 and 56 are amended accordingly.

No new matter is added by these amendments.

II. Rejections Under 35 U.S.C. §102

Claims 1-61 stand rejected under 35 U.S.C. §102 as anticipated by U.S. Patent No. 4,943,590, to Boegesoe and U.S. Patent No. 4,136,193 to Boegesoe. In the final Office Action, the Examiner states that "[t]he pharmaceutical compositions comprising citalopram including tablets and capsules are disclosed by both the references (see Patent 4,943,590 col. 8, line 55 to col. 9, line 48 as well as Patent 4,136,193 col. 7, line 64 to col. 8, line 62)."

It is respectfully submitted that in view of the above amendments and the accompanying Declaration of Hans Petersen (the "Petersen Declaration"), the claimed invention is not anticipated by the prior art. The claims as now presented are limited to crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40μm (claims 16-19, 44 and 45), methods of forming crystallized salts of citalopram having a median particle size of at least 40μm (claims 20-33 and 46-58), tablets formed by direct compression comparing crystallized salts of citalopram having a median particle size of at least 40μm (claims 1, 4-10, 12, 13 and 36-43), and methods of manufacturing tablets comprising crystallized salts of citalopram having a median particle size of at least 40 μm (claims 59 and 61).

It is basic patent law that "[f]or a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art." *See Motorola Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997). Although the disclosure requirement of anticipation "presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there." *Id.* at 1490 (emphasis added). *See also Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673, 1679 (Fed. Cir.), *cert. denied*, 121 S.Ct. 1226 (2000) (invalidity by anticipation requires

that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation.")

In this case, citalopram salt crystals having a median particle size of at least 40μm are nowhere mentioned in the cited '590 and '193 patents, and under principles of patent law cannot be read into these references. Since this element of the claims is not present in the cited art, the claimed invention, including crystals, tablets, crystallization methods, and methods of manufacturing dosage forms, all requiring citalopram salt crystals with the claimed median particle size, is not anticipated.

The Petersen Declaration establishes that citalopram salt crystals having a median particle size of at least 40 μm are not inherent in the prior art. According to Hans Petersen, all known prior art methods of forming citalopram crystals (including the method in the '590 patent) formed crystals having a median particle size of less than 40μm. The only known prior art crystallization methods (disclosed in the '590 and '884 patents) do not allow one of ordinary skill in the art to form crystals of the claimed size.[1]

There are additional grounds of patentability for the crystallization method claims. Claims 20-33 and 46-58 also recite particular method steps that are nowhere disclosed or suggested in the '590, '193 or '884 patents. The crystallization method claims recite cooling steps and the step of seeding crystallization with crystals of citalopram salt. There is no description or suggestion of these method steps in the '590, '193 or '884 patents.

[1] As stated in the Petersen Declaration, the '193 patent does not describe <u>any</u> methods of making a crystallized salt of citalopram. In Example 3, at col. 6, l. 7 to col. 7, l. 33, citalopram is formed as an oil (see col. 7, l. 21-25). The corresponding oxalate salt is formed. However, the oxalate does not form as a crystal. *See* paragraph 4 of the Declaration ("The '193 patent does not describe any methods of making crystallized salts of Citalopram.")

The '590 patent describes crystallizations of citalopram in Example 3. According to this procedure, citalopram base is dissolved in a 2:1 mixture of 2-propanol and methanol, and an equivalent amount of gaseous hydrogen bromide is added. The mixture is left overnight and the precipitated citalopram hydrobromide is filtered off and dried. However, the crystallization method of the '590 patent does not include the particular steps recited in method claim 20 in this application, of cooling the solution to a second temperature; seeding the solution by adding of crystals of citalopram salt; holding the solution at the second temperature; and controlled cooling the solution down to a third temperature.

U.S. Patent No. 4,650,884 also discloses methods of forming crystallized citalopram salts. According to the method of the '884 patent, citalopram base is dissolved in a solvent, gaseous hydrogen bromide is added, and the mixture is left overnight to form crystals. The resulting crystals are filtered and washed with hexane and acetone, and dried at 45°C. The crystals are then dissolved in water at about 55°C, treated with charcoal and filtered, cooled to 20°C and left overnight for crystallization after addition of seed crystals. The resulting crystals are filtered, washed with water and dried. The remaining crystals are then dissolved in a solvent mixture, treated with charcoal, filtered, cooled to 20°C and left overnight for crystallization. The resulting crystals are filtered, washed with a solvent mixture, and dried. The remaining crystals are then dissolved in a solvent mixture, treated with charcoal, filtered and cooled to 20°C. After addition of seed crystals, hexane is added slowly during 1 hour and the mixture is left overnight for crystallization. The resulting crystals are filtered, washed with a solvent mixture of acetone and hexane, and dried.

As stated in paragraph 15 of the Declaration, the crystallization method of the invention is a controlled, slower crystallization resulting in low degrees of supersaturation and

low nucleation rates relative to the particle growth rate, resulting in larger crystals than were formed by previous crystallization methods. The crystallization method described in the '590 patent does not include the step of a controlled cooling of the solution down to a third temperature.

In view of the action taken and arguments made, it is believed that the above referenced rejections have been overcome, and it is respectfully requested that the rejections be withdrawn.

III. Rejections Under 35 U.S.C. §103

Claims 1-61 stand rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 6,147,072, to Bymaster. The Examiner states as follows in the final Office Action:

> Regarding obviousness rejection, the examiner does not agree with the applicants arguments that Bymaster does not teach or provide any motivation to prepare the claimed dosage form (tablet by direct compression). Bymaster teaches that the adjunctive therapy of the prevent invention may be administered together, in a single dosage form, or may be administered separately (see col. 9, lines 30-38). Bymaster also teaches preparing tablets by direct compression (see col. 10, line 31) as well as preparing capsules (see col. 10, line 24).

Applicants respectfully traverse the obviousness rejections, on the grounds that the claims as now presented require crystallized salts of citalopram having a median particle size of at least 40μm. Claims 16-19, 44 and 45 are directed to the crystals themselves, claims 20-33 and 46-58 are directed to methods of forming the crystallized salts, claims 1, 4-10, 12, 13 and 36-43 are directed to tablets formed by direct compression comprising the crystallized salts, and claims 59 and 61 are directed to methods of manufacturing tablets comprising the crystallized salts.

As noted above and as supported by the Petersen Declaration, crystals of a pharmaceutically acceptable salt of citalopram having the claimed median particle size are novel and non-obvious over the prior art cited in the anticipation rejection (U.S. Patent Nos. 4,943,590 and 4,136,193), and over U.S. Patent No. 4,650,884. The reference cited in the obviousness rejection, Bymaster, provides no additional teaching or suggestion of crystallized salts of citalopram having the claimed median particle size. As correctly set out by the Examiner in the first office action, Bymaster describes a combination therapy for treatment of psychoses, which can be formed in tablet or capsule dosage form, according to the disclosure at column 10, lines 31-56. However, Bymaster does not teach nor suggest the claimed crystals, nor a method for manufacturing the crystals. In fact, Bymaster is silent about the specific structural form of citalopram, and is silent about methods of crystallizing salts of citalopram. The claims are not obvious because the cited art fails to describe or suggest the claimed crystallized salts or tablets, or to describe or suggest the claimed methods.

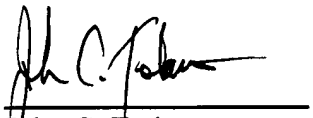
In view of the action taken and arguments made, it is believed that the above referenced obviousness rejections have been overcome, and it is respectfully requested that the rejections be withdrawn.

IV. Conclusion

In view of the foregoing, it is believed that all pending claims 1, 4-10, 12, 13, 16-33, 36-59 and 61 are neither anticipated by nor obvious over the art of record. Claims 1, 4-10, 12, 13, 16-33, 36-59 and 61 are now believed to be in condition for allowance.

Favorable action is earnestly solicited.

Respectfully submitted,



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PATRICIA A. RUBIO Patricia A. Rubio
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07278
PATENT TRADEMARK OFFICE

File No. 5432/0I004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ken LILEJEGREN *et al.*

Serial No.: 09/730,380 Group Art Unit: 1625

Filed: December 5, 2000 Examiner: C. Aulakh

For: PHARMACEUTICAL COMPOSITION CONTAINING CITALOPRAM

PENDING CLAIMS
AFTER ACCOMPANYING AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

1. (Twice Amended) A tablet comprising crystals of a pharmaceutically acceptable salt of citalopram, wherein the median particle size of the crystals is at least 40 μm, which is prepared by direct compression of the pharmaceutically acceptable salt and pharmaceutically acceptable excipients.

4. (Twice Amended) The tablet according to claim 1 which does not contain a binder.

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5. (Twice Amended) The tablet according to claim 1 which contains 2-60% w/w active ingredient calculated as citalopram base.

6. (Twice Amended) The tablet according to claim 1 which contains a filler selected from lactose, sugars, calcium phosphates, starch, modified starches, microcrystalline cellulose, calcium sulfate and calcium carbonate.

7. (Twice Amended) The tablet according to claim 6, wherein the filler is a microcrystalline cellulose.

8. (Twice Amended) The tablet according to claim 1 which contains a lubricant selected from metallic stearates, stearic acid, wax, hydrogenated vegetable oil, talc and colloidal silica.

9. (Twice Amended) The tablet according to claim 8, wherein the lubricant is magnesium stearate or calcium stearate.

10. (Twice Amended) The tablet according to claim 1 which is substantially free of lactose.

12. (Twice Amended) The tablet according to claim 1 wherein the pharmaceutically acceptable salt is citalopram hydrobromide or citalopram hydrochloride.

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13. (Twice Amended) The tablet according to claim 12, wherein the pharmaceutically acceptable salt is citalopram hydrobromide.

16. (Amended) Crystals of a pharmaceutically acceptable salt of citalopram wherein the median particle size of the crystals is at least 40μm.

17. (Amended) Crystals according to claim 16, wherein the crystals are of citalopram hydrobromide or citalopram hydrochloride.

18. (Amended) Crystals according to claim 17, wherein the crystals are of citalopram hydrobromide.

19. (Amended) Crystals according to claim 16, wherein the median particle size of the crystals is in the range of 40 - 200μm.

20. (Twice Amended) Method for manufacture of crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40μm, said method comprising the steps of forming a solution of a pharmaceutically acceptable salt of citalopram in a solvent system at a first temperature, cooling the solution to a second temperature, seeding the solution by addition of crystals of said citalopram salt, followed by holding the solution at said second temperature and a controlled cooling the solution down to a third temperature, and isolating said crystals.

21. (Amended) The method according to claim 20, wherein the median particle size of the crystals is in the range of 40 - 200μm.

22. (Twice Amended) The method according to claim 20, wherein the pharmaceutically acceptable salt of citalopram is citalopram hydrobromide or citalopram hydrochloride.

23. (Twice Amended) The method according to claim 22, wherein the pharmaceutically acceptable salt of citalopram is citalopram hydrobromide.

24. (Amended) The method according to claim 20, wherein the solvent system comprises one or more alcohols and optionally water.

25. (Amended) The method according to claim 24, wherein the solvent system is a mixture of methanol and water.

26. (Amended) The method according to claim 25 wherein the methanol:water weight ratio is in the range of 5:1 to 50:1.

27. (Amended) The method according to claim 20 wherein the solvent:solute weight ratio is in the range of 0.5:1 to 5:1.

28. (Amended) The method according to claim 20 wherein said first temperature is in the range between 50°C and the refluxing temperature of the solvent system.

29. (Amended) The method according to claim 20 wherein said second temperature is in the range of 20-40°C.

30. (Twice Amended) The method according to claim 20 wherein the step of holding the solution at said second temperature is from 30 minutes to 7 days .

31. (Amended) The method according to claim 20 wherein said third temperature is in the range of 0-20°C.

32. (Amended) The method according to claim 20 wherein said controlled cooling down is a gradual cooling down over a time span in the range of 5 minutes to 6 hours.

33. (Twice Amended) The method according to claim 20 wherein the step of isolating the crystals of a pharmaceutically acceptable salt of citalopram is performed by filtration.

36. (Amended) The tablet of claim 1, which contains 10-40% w/w active ingredient calculated as citalopram base.

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37. (Amended) The tablet of claim 1, which contains 15-25% w/w active ingredient calculated as citalopram base.

38. (Amended) The tablet of claim 6, wherein said filler is a sugar selected from the group consisting of sorbitol, mannitol, dextrose and sucrose.

39. (Amended) The tablet of claim 6, wherein said filler is a calcium phosphate selected from the group consisting of dibasic, tribasic, hydrous and anhydrous calcium phosphate.

40. (Amended) The tablet of claim 8, wherein said lubricant is a metallic stearate selected from the group consisting of magnesium, calcium and sodium stearate.

41. (Amended) The tablet of claim 1, wherein the crystals have a median particle size of 40-200 μm.

42. (Amended) The tablet of claim 1, wherein the crystals have a median particle size of 45-150μm.

43. (Amended) The tablet of claim 1, wherein the crystals have a median particle size of 50-100μm.

44. Crystals according to claim 19, wherein the median particle size of the crystals is in the rage of 45-150μm.

45. Crystals according to claim 19, wherein the median particle size of the crystals is in the rage of 50-120μm.

46. The method according to claim 21, wherein the median particle size of the crystals in the range of 45-150μm.

47. The method according to claim 21, wherein the median particle size of the crystals in the range of 50-120μm.

48. The method according to claim 26, wherein the methanol:water weight ratio is in the range of 10:1 to 30:1.

49. The method according to claim 26, wherein the methanol:water weight ratio is in the range of 15:1 to 25:1.

50. The method according to claim 27, wherein the solvent:solute weight ratio is in the range of 0.7:1 to 2:1.

51. The method according to claim 27, wherein the solvent:solute weight ratio is in the range of 0.9:1 to 1.5:1.

52. The method according to claim 28, wherein said first temperature is in the range between 60°C and the refluxing temperature.

53. The method according to claim 28, wherein said first temperature is in the range between 64°C and the refluxing temperature.

54. The method according to claim 29, wherein said second temperature is in the range of 25-35°C.

55. (Amended) The method according to claim 30, wherein the step of holding the solution at said second temperature is from 1 hour to 4 days.

56. (Amended) The method according to claim 30, wherein the step of holding the solution at said second temperature is from 12 to 36 hours.

57. The method according to claim 32, wherein said time span is in the range of 15 minutes to 4 hours.

58. The method according to claim 32, wherein said time span is in the range of 30 minutes to 2 hours.

59. A method for manufacturing a citalopram dosage form, which comprises

providing a solution of a pharmaceutically acceptable salt of citalopram in a suitable solvent system at a first temperature;

cooling said solution to a second temperature below said first temperature;

seeding said solution with crystals of said citalopram salt;

holding said solution at said second temperature for a predetermined period of time;

cooling said solution to a third temperature that is lower than said second temperature to form citalopram crystals having a median particle size of at least 40μm;

isolating said crystals from said solution; and

directly compressing a predetermined quantity of crystals into a tablet.

61. The method of claim 59 which comprises compressing a pharmaceutically acceptable excipient with said crystals.

File No. 5432/0I004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ken LILEJEGREN *et al.*

Serial No.: 09/730,380 Group Art Unit: 1625

Filed: December 5, 2000 Examiner: C. Aulakh

For: PHARMACEUTICAL COMPOSITION CONTAINING CITALOPRAM

MARKUP ACCOMPANYING AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

IN THE CLAIMS

Please amend claims 1, 4-10, 12, 13, 20, 22, 23, 30, 33, 36-43, 55 and 56 as follows.

1. (Twice Amended) A [solid unit dosage form] tablet comprising crystals of a pharmaceutically acceptable salt of citalopram, wherein the median particle size of the crystals is at least 40 μm, which is prepared by direct compression of [a mixture of citalopram base or a] the pharmaceutically acceptable salt and pharmaceutically acceptable excipients[, or by filling of said mixture in a hard gelatine capsule].

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4. (Twice Amended) The [solid unit dosage form] tablet according to claim 1 which does not contain a binder.

5. (Twice Amended) The [solid unit dosage form] tablet according to claim 1 which contains 2-60% w/w active ingredient calculated as citalopram base.

6. (Twice Amended) The [solid unit dosage form] tablet according to claim 1 which contains a filler selected from lactose, sugars, calcium phosphates, starch, modified starches, microcrystalline cellulose, calcium sulfate and calcium carbonate.

7. (Twice Amended) The [solid unit dosage form] tablet according to claim 6, wherein the filler is a microcrystalline cellulose.

8. (Twice Amended) The [solid unit dosage form] tablet according to claim 1 which contains a lubricant selected from metallic stearates, stearic acid, wax, hydrogenated vegetable oil, talc and colloidal silica.

9. (Twice Amended) The [solid unit dosage form] tablet according to claim 8, wherein the lubricant is magnesium stearate or calcium stearate.

10. (Twice Amended) The [solid unit dosage form] tablet according to claim 1 which is substantially free of lactose.

12. (Twice Amended) The [solid unit dosage form] tablet according to claim 1 wherein the [active ingredient] pharmaceutically acceptable salt is citalopram hydrobromide or citalopram hydrochloride.

13. (Twice Amended) The [solid unit dosage form] tablet according to claim 12, wherein the [active ingredient] pharmaceutically acceptable salt is citalopram hydrobromide.

20. (Twice Amended) Method for manufacture of crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40μm [wherein], said method comprising the steps of forming a solution of a pharmaceutically acceptable salt of citalopram in a [suitable] solvent system at a first temperature [is first cooled down], cooling the solution to a second temperature [then seeded], seeding the solution by addition of crystals of said citalopram salt, followed by [a] holding [time] the solution at said second temperature and a controlled cooling the solution down to a third temperature [whereupon], and isolating said crystals [are isolated by conventional solid/liquid separation techniques].

22. (Twice Amended) The method according to claim 20, wherein the [dissolved substance] pharmaceutically acceptable salt of citalopram is citalopram hydrobromide or citalopram hydrochloride.

23. (Twice Amended) The method according to claim 22, wherein the [dissolved substance] pharmaceutically acceptable salt of citalopram is citalopram hydrobromide.

30. (Twice Amended) The method according to claim 20 wherein [said] the step of holding [time] the solution at said second temperature is [in the range of] from 30 minutes to 7 days .

33. (Twice Amended) The method according to claim 20 wherein [said isolation of] the step of isolating the crystals of a pharmaceutically acceptable salt of citalopram [from the mother liquor] is performed by filtration.'

36. (Amended) The [solid unit dosage form] tablet of claim 1, which contains 10-40% w/w active ingredient calculated as citalopram base.

37. (Amended) The [solid unit dosage form] tablet of claim 1, which contains 15-25% w/w active ingredient calculated as citalopram base.

38. (Amended) The [solid unit dosage form] tablet of claim 6, wherein said filler is a sugar selected from the group consisting of sorbitol, mannitol, dextrose and sucrose.

40. (Amended) The [solid unit dosage form] tablet of claim 8, wherein said lubricant is a metallic stearate selected from the group consisting of magnesium, calcium and sodium stearate.

41. (Amended) The [solid unit dosage form] tablet of claim [15] 1, wherein the [active ingredient is in the form of] crystals [with] have a median particle size of 40-200μm.

42. (Amended) The [solid unit dosage form] tablet of claim [15] 1, wherein the [active ingredient is in the form of] crystals [with] have a median particle size of 45-150μm.

43. (Amended) The [solid unit dosage form] tablet of claim [15] 1, wherein the [active ingredient is in the form of] crystals [with] have a median particle size of 50-100μm.

55. (Amended) The method according to claim 30, wherein [said] the step of holding [time] the solution at said second temperature is [in the range of] from 1 hour to 4 days.

56. (Amended) The method according to claim 30, wherein [said] the step of holding [time] the solution at said second temperature is [in the range of] from 12 to 36 hours.

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